Selective IgE deficiency, immune dysregulation, and autoimmunity

Eli Magen, M.D.,[1,2,3] Menachem Schlesinger, M.D.,[2] Michael David, M.D.,[4] Itzhak Ben-Zion, M.D.,[1] and Daniel Vardy, M.D., M.Sc.[1,3]

ABSTRACT

Selective IgE deficiency (IgED) is currently defined as a significant decrease in serum levels of IgE (<2 kIU/L) in a patient whose other immunoglobulin levels are normal. There are no published large-scale epidemiological studies regarding the prevalence of and clinical features of IgED. In the population-based case–control study, we investigated clinical and laboratory characteristics of patients with IgED. Case samples were drawn from all subjects (n = 18487), with serum total IgE measurement during 2012 at Leumit Health Care Services (Israel) and had serum total IgE of <2 kIU/L. The control group was randomly sampled from the remaining 18,261 subjects with a case–control ratio of four controls for each case (1:4). Comorbid diseases were identified by specific International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes given by the corresponding board-certificated physicians. Two hundred twenty-six subjects showed serum total IgE levels of <2 kIU/L; 68 (30.9%) were between the ages of 4 and 12 years (children) and 250 (69.1%) were ≥12 years old (adults). Matched control groups were selected for each age group. The children group was characterized by higher prevalence of asthma and hyperreactive airways disease; and both children and adult groups had significantly higher prevalence of chronic sinusitis, otitis media, autoimmune, and oncological diseases than their respective controls. Undetectable serum total IgE may serve as a marker of immune dysregulation and autoimmunity.

(Allergy Asthma Proc 35:e27–e33, 2014; doi: 10.2500/aap.2014.35.3734)

After the discovery of IgE, there was great success in understanding its role in immediate hypersensitivity, host defense, parasitic infection, and immune surveillance; however, the pathophysiological consequences of IgE hypogammaglobulinemia remain understudied. Compared with the major circulating immunoglobulins (IgG, IgA, and IgM), IgE is the least abundant of the human immunoglobulin classes and was, accordingly, the last to be discovered in the late 1960s.[1] The concentration of IgE in normal human sera is between 10 and 400 ng/mL, and its half-life in the circulation, is estimated at 2–2.5 days, whereas serum IgG has a half-life of ~3 weeks.[2] IgE is best known for its pathological effects in allergic diseases and the beneficial role of IgE in host defense against parasitic infections, in particular, against helminth infections.[3]

There have been few studies on patients with a low or undetectable serum total IgE. Normal levels of IgE are highly variable within the population.[4] Selective IgE deficiency (IgED) is currently defined as a significant decrease in serum levels of IgE (<2 kIU/L) in a patient whose other immunoglobulin levels are normal or diminished (mixed IgED).[5] Mainly, it is a laboratory finding and the vast majority of affected individuals are asymptomatic.[6] There are no published large-scale epidemiological studies regarding the prevalence of IgE hypogammaglobulinemia and IgED.

In this population-based case–control study, we attempted to investigate clinical and laboratory characteristics of patients with IgED.

MATERIALS AND METHODS

Data Source

This is a retrospective matched case–control study, based on data from Leumit Health Care Services (Israel) Database. The health maintenance organization covers ~720,000 residents of Israel, and its electronic database includes comprehensive information on the insured population, such as demographic data, records of clinical visits, laboratory tests, performed at a single centralized laboratory, and diagnostic codes using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This database was used to obtain information on diagnoses and laboratory results by means of cross-linkage using a unique patient identifier.

This study was approved by the Barzilai Medical Center and Leumit Health Care Services Institutional Review Committee.

From [1]Leumit Health Care Services, Ashdod, Israel, [2]Allergy and Clinical Immunology Unit, Barzilai Medical Center, Ashkelon, Israel, [3]Ben-Gurion University of Negev, Ashkelon, Israel, and [4]Rabin Medical Center, Petah Tikva, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Eli Magen, M.D., Allergy and Clinical Immunology Unit, Barzilai Medical Center, Ben Gurion University of Negev, Ashkelon, Israel
E-mail address: allergologycom@gmail.com

Subjects

Inclusion Criteria. Inclusion criteria included all subjects, having any allergy-related symptoms and/or those requesting antiallergy medications and performed serum total IgE measurement during 2012 at Leumit Health Care Services.

The case group samples were drawn from the full study population (n = 18,487). We included all cases with serum total IgE of <2 kIU/L, which were further divided into two groups according to the age of the subjects: (1) aged 4–11 years old and (2) aged ≥12 years old. The control group was randomly sampled from the remaining 18,261 subjects with a case–control ratio of four controls for each case (1:4). The randomization was performed using the Epi Info 6 software (Atlanta, GA) using simple random sampling.

The case and control group patients presented with various complaints of suspected allergic diseases. The diagnosis of allergic disease was performed by the board-certified family physicians, allergists, dermatologists, and pulmonologists. Symptoms and signs consistent with allergic conjunctivitis, rhinitis, sinusitis, bronchial asthma, atopic dermatitis, contact dermatitis, urticaria, angioedema, food allergies, and recurrent infections were documented. Usually, the patients were initially assessed by primary care physicians, dermatologists, and pulmonologists and in the cases of persistent or severe symptoms, they were referred to allergists/immunologists for further evaluation and treatment. Based on history and clinical picture, complete blood count, serum biochemistry, thyroid function tests, antinuclear antibodies, and total serum IgE levels were tested in these patients. Total serum IgE level analysis was performed to rule out atopic state and/or as a part of the humoral immune system function assessment in the cases of recurrent infectious diseases in a patient.

The comorbid diseases, diagnosed by the corresponding board-certificated physicians during ≤5 years before serum total IgE testing, were identified and retrieved from Leumit Health Care Services electronic database using specific ICD-9-CM diagnostic codes.

Exclusion Criteria. Exclusion criteria included selective IgA deficiency, common variable immunodeficiency (CVID), ataxia telangiectasia, human immunodeficiency virus/acquired immunodeficiency syndrome, chronic systemic corticosteroid therapy, or on any other form of immunosuppressive therapy during the 4 weeks before serum total IgE measurement.

Selective IgAD was diagnosed by the following criteria: male or female patient >4 years of age who has a serum IgA of <7 mg/dL (0.07 g/L) but normal serum IgG and IgM, in whom other causes of hypogammaglobulinemia have been excluded.

CVID was diagnosed by following criteria: male or female patient with a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA and who fulfills all the following criteria: (1) onset of immunodeficiency at >2 years of age, (2) absent isohemagglutinins and/or poor response to vaccines, and (3) defined causes of hypogammaglobulinemia have been excluded.

Total IgE Measurement

Serum samples were analyzed for total IgE levels using the immunometric assay by the Immulite 2000 system (DPC; Global Siemens Healthcare, Erlangen, Germany). Total serum IgE ranged from 2 to 2000 IU/mL for the whole study population. Complete data for analysis of total serum IgE were available for 18,247 subjects. In all cases of serum total IgE < 2 kIU/L, analyses of other serum immunoglobulins were routinely performed to exclude humoral immunodeficiency.

IgM, IgA, and IgG Immunoglobulin Measurements

Serum immunoglobulins (IgM, IgA, IgG, IgG1, IgG2, IgG3, and IgG4) were measured by nephelometry (BN II System; Dade Behring, Deerfield, IL). All 226 case subjects had data available for measurements of these immunoglobulins.

Statistical Analyses

Differences in demographic and clinical characteristics between the groups were analyzed using χ^2- or Fisher's exact test when appropriate. The multiple regression analyses adjusted for sex and age (odds ratio [OR] with 95% confidence intervals) were performed separately for each group of comorbidity (autoimmune diseases, chronic sinusitis + recurrent otitis, and oncological diseases), to exclude the potential bias. To deal with possible multiplicity issues, we applied a Bonferroni correction testing at a significance level of α (0.05)/k (number of tests) to lower the chance of a type 1 error. Analyses were conducted using the Statistical Package SPSS 16.0. (StatSoft, Inc., Tulsa, OK).

RESULTS

Demographic and Laboratory Characteristics of Cases and Controls

A total number of 18,487 subjects aged 4–69 years old were identified as having performed a serum total IgE test between January 1 and December 31, 2012 comprising 6851 (36%) male subjects and 11,636 (64%) female subjects without a significant age difference.

Table 1 **Clinical and laboratory characteristics of subjects aged 4–11 years old**

	Case A Subjects (n = 68)	Control A subjects (n = 250)	p Value	Multiple Logistic Regression Model OR (95% CI)
Sex: female, %	43 (63.2%)	152 (60.8%)	0.675	
Age (yr)	6.8 ± 2.5	6.9 ± 2.8	0.789	
Body mass index, kg/m^2	24.1 ± 3.9	24.4 ± 3.7	0.558	
Total IgE (kIU/L)	0.3 ± 0.4	129.4 ± 79.6	<0.001	
WBC (cell/mm^3)	9.7 ± 4.2	9.2 ± 3.9	0.357	
Lymphocytes (cell/mm^3)	2.9 ± 1.5	3.1 ± 1.7	0.377	
Eosinophils (cell/mm^3)	0.34 ± 0.18	0.38 ± 0.21	0.153	
Basophils (cell/mm^3)	0.17 ± 0.12	0.19 ± 0.14	0.283	
Platelets (cell × 10^8/mm^3)	262 ± 137	271 ± 125	0.607	
Chronic infectious diseases (no.)	50	25	<.001	20.7 (8.7–42.5); $p < 0.001$
Chronic sinusitis, n (%)	19 (27.9%)	11 (4.4%)	<0.001	6.1 (2.2–15.1); $p < 0.001$
Rec. otitis media, n (%)	31 (45.6%)	14 (5.6%)	<0.001	11.3 (3.9–23.4); $p < 0.001$
Allergic diseases (no.)	51	106	0.679	3.5 (2.1–6.4); $p < 0.001$
Allergic rhinitis, n (%)	5 (7.3%)	31 (12.4%)	0.384	0.4 (0.1–1.3); $p = 0.391$
Asthma + HRAD, n (%)	18 (26.5%)	17 (6.8%)	<0.001	3.1 (1.9–8.3); $p < 0.001$
Atopic dermatitis, n (%)	19 (27.9%)	51 (20.4%)	0.749	1.2 (0.5–2.1); $p = 0.529$
Contact dermatitis, n (%)	1 (1.5%)	2 (0.8%)	0.513	1.3 (0.2–17.1); $p = 0.782$
Food allergy, n (%)	8 (11.8%)	5 (2%)	0.001	5.1 (1.5–16.2); $p = 0.003$
Autoimmune diseases (no.)	5	0	<0.001	35.2 (1.7–536.3); $p = 0.024$
Chronic urticaria, n (%)	2 (2.9%)	0	0.045	15.7 (0.7–315.4); $p = 0.063$
Psoriasis, n (%)	1 (1.5%)	0	0.213	9.3 (0.2–229.5); $p = 0.295$
Celiac disease, n (%)	1 (1.5%)	0	0.213	9.3 (0.2–229.5); $p = 0.295$
Type I diabetes mellitus, n (%)	1 (1.5%)	0	0.213	9.3 (0.2–229.5); $p = 0.295$
ITP, n (%)	0	0	1	2.1 (0.04–162.1); $p = 0.731$

Significant OR after Bonferroni correction ($p < 0.004$; $\alpha = 0.05/12$ tests = 0.0042).
ITP = immune thrombocytopenic purpura; HRAD = hyperreactive airways disease; OR = odds ratio; CI = confidence interval; WBC = white blood cell count.

From the total number of 226 subjects with serum total IgE < 2 kIU/L, there were 68 (30.9%) subjects aged 4–11 years old (children group) and 158 (69.1%) subjects aged ≥12 years old (adult group). The corresponding children control group consisted of 250 subjects, and the adult control group included 600 subjects. Except for serum total IgE levels, there were no differences between the cases and controls in the demographic and laboratory characteristics (Tables 1 and 2). In both children and adult groups, there were more female subjects than male subjects (43 [63.2%] and 113 [71.5%], respectively). No differences between male and female patients in both groups were observed with respect to clinical and laboratory characteristics.

Chronic Sinusitis, Recurrent Otitis Media, and IgED

Table 1 describes the characteristics of the study population. Separate analysis of children and children control groups in the 4- to 11-year-old patients revealed significantly higher prevalence of chronic sinusitis (27.9%; $p < 0.001$) and otitis media (45.6%; $p < 0.001$) at IgE levels of <2 kIU/L. As summarized in the Table 2, a separate analysis of adult and adult control groups in the ≥12-year-old patients also showed a higher prevalence of chronic sinusitis (41 [25.9%]; $p < 0.001$) and otitis media (10 [6.3%]; $p < 0.001$) in case subjects than in corresponding control subjects. In the children group, the odds of having chronic sinusitis was 6.1 (2.2- 15.1; $p < 0.001$) and recurrent otitis media was 11.3 (3.9–23.4; $p < 0.001$) than in the children control group (Table 1). In the adult group, the odds of having chronic sinusitis was 14.9 (7.8- 13.4; $p < 0.001$) and recurrent otitis media was 12.1 (2.6–21.1; $p < 0.001$) compared with the adult control group (Table 2).

Allergic Diseases and IgED

In the children group, there was a higher prevalence of asthma and hyperreactive airways disease (26.5% versus 6.8%; $p < 0.001$ in children control group). The children group was also characterized by a higher

Table 2 **Clinical and laboratory characteristics of subjects aged ≥12 years old**

	Case B Subjects (n = 158)	Control B Subjects (n = 600)	p Value	Multiple Logistic Regression Model OR (95% CI)
Sex: female, %	113 (71.5%)	418 (69.7%)	0.889	
Age (yr)	44.3 ± 20.4	43.6 ± 21.2	0.741	
Body mass index, kg/m^2	26.2 ± 3.5	26.6 ± 3.4	0.153	
Total IgE (kIU/L)	0.3 ± 0.2	112.7 ± 71.8	<0.001	
WBC (cell/mm^3)	7.1 ± 3.4	6.9 ± 3.5	0.570	
Lymphocytes (cell/mm^3)	2.4 ± 1.3	2.3 ± 1.6	0.509	
Eosinophils (cell/mm^3)	0.31 ± 0.14	0.32 ± 0.17	0.536	
Basophils (cell/mm^3)	0.15 ± 0.11	0.17 ± 0.14	0.091	
Platelets (cell × 10^8/mm^3)	259 ± 124	265 ± 129	0.602	
Chronic infectious diseases, n	74	21	<0.001	19.1 (11.2–37.9); $p < 0.001$
Chronic sinusitis, n (%)	41 (25.9%)	19 (3.1%)	<0.001	14.9 (7.8–13.4); $p < 0.001$
Rec. otitis media, n (%)	10 (6.3%)	2 (0.3%)	<0.001	12.1 (2.6–21.1); $p < 0.001$
Allergic diseases, n	39	311	0.442	0.21 (0.14–0.39); $p < 0.001$
Allergic rhinitis, n (%)	5 (3.1%)	173 (28.8%)	<0.001	0.06 (0.01–0.2); $p < 0.001$
Asthma, n (%)	15 (9.5%)	76 (12.7%)	0.335	0.59 (0.3–1.1); $p = 0.419$
Atopic dermatitis, n (%)	6 (3.8%)	27 (4.5%)	0.828	0.71 (0.2–1.8); $p = 0.874$
Contact dermatitis, n (%)	12 (7.5%)	35 (5.8%)	0.457	1.14 (0.6–2.3); $p = 0.595$
Food allergy, n (%)	1 (0.6%)	0	0.208	9.7 (0.4–255.7); $p = 0.386$
Autoimmune diseases, n	126	61	>0.001	27.1 (14.3–43.8); $p < 0.001$
Hashimoto's thyroiditis, n (%)	23 (14.6%)	8 (1.3%)	<0.001	9.8 (3.9–21.5); $p < 0.001$
Graves' disease, n (%)	9 (5.7%)	3 (0.5%)	<0.001	8.1 (1.9–38.7); $p < 0.001$
Pernicious anemia, n (%)	11 (6.9%)	2 (0.6%)	<0.001	17.2 (2.1–89.1); $p < 0.001$
Chronic urticaria, n (%)	30 (19%)	5 (0.8%)	<0.001	22.5 (8.5–64.1); $p < 0.001$
Psoriasis, n (%)	13 (8.2%)	11 (1.8%)	<0.001	3.9 (1.7–9.2); $p < 0.001$
Seborrheic dermatitis, n (%)	6 (3.8%)	7 (1.2%)	0.034	2.6 (0.8–9.3); $p = 0.054$
Dermatitis herpetiformis, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Alopecia areata, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Vitiligo, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Lichen planus, n (%)	1 (0.6%)	1 (0.3%)	0.373	2.9 (0.1–55.8); $p = 0.462$
Sarcoidosis, n (%)	3 (1.9%)	0	0.009	21.5 (1.2–495.4); $p = 0.035$
Erythema nodosum	2 (1.3%)	0	0.043	15.2 (0.7–329.2); $p = 0.062$
Rheumatoid arthritis, n (%)	2 (1.3%)	3 (0.5%)	0.279	1.9 (0.3–12.6); $p = 0.469$
Sjögren's disease, n (%)	2 (1.3%)	2 (0.6%)	0.193	2.4 (0.3–24.1); $p = 0.294$
Dermatomyositis, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Fibromyalgia, n (%)	7 (4.4%)	1 (0.3%)	>0.001	21.6 (2.1–185.5); $p < 0.001$
Immune-mediated neuropathy, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Addison disease, n (%)	2 (1.3%)	0	0.043	14.1 (0.7–343.5); $p = 0.071$
Type I diabetes mellitus, n (%)	4 (2.5%)	0	0.002	28.3 (1.9–172.7); $p = 0.032$
Chronic fatigue syndrome, n (%)	6 (3.8%)	1 (0.3%)	>0.001	18.5 (2.3–171.4); $p = 0.009$
Oncological diseases, n	17	9	>0.001	5.9 (2.7–14.2); $p < 0.001$
Epithelial cancers, n (%)	7 (4.4%)	7 (1.1%)	0.014	3.1 (1.2–10.5); $p = 0.028$
CLL/lymphoma, n (%)	5 (3.1%)	2 (0.3%)	0.005	7.9 (1.4–46.7); $p = 0.015$
Multiple myeloma, n (%)	2 (1.3%)	0	0.043	14.7 (0.8–269.3); $p = 0.062$
Mycosis fungoides, n (%)	1 (0.6%)	0	0.208	9.2 (0.3–251.8); $p = 0.307$
Myeloproliferative diseases, n (%)	2 (1.3%)	0	0.043	14.1 (0.7–343.5); $p = 0.071$

Significant OR after Bonferroni correction ($p < 0.0016$; $\alpha = 0.05/32$ tests = 0.0016).
CLL = chronic lymphocytic leukemia; SLE = systemic lupus erythematosus; OR (95% CI) = odds ratio, 95% confidence interval between case B and control B subjects; WBC = white blood cell count.

prevalence of food allergy (11.8% versus 2%; $p = 0.001$ in the children control group; Table 1). Among the ≥12-year-old subjects, the adult control group had a significantly greater prevalence of allergic rhinitis (28.8% versus 3.1%; $p < 0.001$; Table 2).

Autoimmune Diseases and IgED

Thyroid diseases were the most common associated autoimmune diseases in patients with IgED; 14.6% of the adult group patients had Hashimoto's thyroiditis compared with 1.3% ($p < 0.001$) in the adult control group (Table 1). The odds of having Hashimoto's thyroiditis was 9.8 (3.9–21.5; $p < 0.001$) and OR of having Graves' disease was 8.1 (1.9–38.7; $p < 0.001$) in the adult group compared with the adult control group subjects.

There were 30 (19%) cases of chronic idiopathic urticaria in the adult group, in contrast with 5 (0.8%) cases in the adult control group ($p < 0.001$). The OR of having chronic idiopathic urticaria with IgED was 22.5 (8.5–64.1; $p < 0.001$).

As it is presented in Tables 1 and 2, the prevalence of other organ-specific and systemic autoimmune diseases was significantly higher in both the children and the adult groups than in the corresponding control groups: the OR of having any autoimmune disease was 35.2 (1.7–536.3; $p = 0$ .024) for the children group compared with the children control and 27.1 (14.3–43.8; $p < 0.001$) for the adult group compared with adult control group.

Oncological Diseases and IgED

The adult group patients were characterized with higher prevalence of oncological diseases than the adult control group (Table 2). The OR of having epithelial or hematologic malignancies was 5.9 (2.7–14.2; $p < 0.001$) for the adult group compared with the adult control group (Table 2).

DISCUSSION

In this study, the clinical characteristics of a relatively large group of patients with IgED, but normal IgM, IgG, and IgA serum levels, were evaluated. There are three findings in this study: (1) in children IgED is associated with a higher rate of chronic rhinosinusitis and bronchial asthma and in both children and adults with recurrent rhinosinusitis and otitis media, (2) several autoimmune diseases are more prevalent in subjects with IgED than in gender- and age-matched controls with normal or high serum IgE levels, and (3) undetectable levels of serum total IgE are an independent predictor of autoimmune and oncological diseases.

IgED is a rare entity, and its association to clinical relevant immunodeficiency is controversial.[7–16] In our outpatient setting, only 226 (1.22%) of 18,487 patients who underwent IgE determination had a serum total IgE level under the detection threshold (2 kIU/L) and none of the patients with IgED in our series showed any data suggesting a familial history of immunodeficiency.

There is very limited information about prevalence of IgED. Some investigators found an incidence of 16.5%, but their threshold was 10 kIU/L[17] and others found 10.5% of patients with IgE levels <2.5 kIU/L.[7] Our incidence is much lower than in the previous studies[7,17]; probably because of the lower threshold of serum total IgE we used to identify patients with IgED. Notably, another group found only 9 (1.4%) patients with IgED of 643 subjects, when their IgE threshold was <2 kIU/L.[18] Notably, in both the children and the adult groups there were more female subjects than male subjects but with similar clinical and laboratory characteristics. It is difficult to explain the observed female predominance; maybe hormonal factors can play some role in the pathophysiology of IgED.

Etiologic factors causing IgED are unknown. Because the levels of other immunoglobulin isotypes are normal in individuals with IgED, the possibility of a selective class switch recombination gene defect to this isotype by the mutagenic activation-induced cytidine deaminase is suggested.[18]

An association between undetectable serum total IgE levels and chronic upper and lower respiratory tract inflammatory diseases was previously checked in other small studies. Higher rates of chronic rhinosinusitis and asthma were observed in adult patients with an undetectable serum total IgE,[7,8,19,20] whereas others studies found no such association.[9,10] The mechanisms underlying the susceptibility to chronic rhinosinusitis and otitis media in children and adults and to asthma in children observed in this study among subjects with IgED are poorly understood. Mucosal immunity creates the first line of defense for the host and is a major component of resistance against respiratory infections. The role of another mucosal immunoglobulin, secretory IgA in controlling respiratory infections is shown in patients with selective IgAD. These patients are more prone to rhinosinusitis, otitis media, tonsillitis, chronic pulmonary infections, and asthma.[21,22]

IgE-secreting plasma cells are located in mucosal tissues of the respiratory tract and in tonsillar and adenoidal tissues[23] and local IgE production in tissues is a major source for allergen-specific IgE.[24] The observations of IgED in association with recurrent respiratory infections may implicate an involvement of this immunoglobulin in respiratory tract defense.[25]

The only animal model of IgED, mice with a targeted deletion of IgE (IgE−/−mice), have no signs of any disease, and their immune system development and function is normal.[26] Therefore, at least for laboratory mice, life is possible in the complete absence of IgE. Nevertheless, lymphotoxin α-deficient mice who ex-

hibit diminished levels of IgE develop Th1-mediated inflammatory airway disease that is nonallergic and noninfectious.[11] This observation indicates that IgE may play a role in the regulation of the respiratory immune response.[11] Furthermore, IgE can enhance immune responses against antigens that are present at low concentrations.[27] In addition, very low quantities of antigens are required to activate mast cells and basophils if antigen-specific IgE is present on the cell surface.[28,29] Mucosal IgE antibodies in nasal mucosal tissue are able to continuously activate mast cells.[30] The presence of subnormal levels of IgE impairs the ability of mast cells to respond normally to airway antigens and induce Th2 development; as a result, Th1 responses predominate and lead to corresponding immunopathology.[6,12] The IgE-mediated FcεRI up-regulation and stabilization appear to be essential for establishing long-lasting memory of mast cells and basophiles.[31] Therefore, failure of mast cells to function as immune sentinels early in infection may play an important role in mediating susceptibility to infection in patients with IgED.[32]

Our results also reflect a significant relationship between IgED and autoimmune diseases. There are no published large-scale epidemiological studies regarding the prevalence of IgED or IgE hypogammaglobulinemia among patients with autoimmune diseases. Only several small studies reported of an increased prevalence of autoimmune diseases in persons with IgED.[7,18] In one case report, alopecia universalis was found to be associated with impaired interleukin-4 production and low serum IgE level.[33] In another study, low or undetectable serum IgE levels were measured in 22 symptomatic adults with primary biliary cirrhosis and in 13 asymptomatic individuals with positive serum mitochondrial antibody tests.[34]

The mechanism underlying the induction of autoimmunity in IgED remains elusive. Probably, by clinical features, selective IgED resembles selective IgAD, where most individuals are clinically asymptomatic, but the defect may be associated with recurrent respiratory and gastrointestinal tract infections/disorders, autoimmunity, and allergies.[35,36] Similarly, ~20% of patients with CVID develop autoimmune complications.[37] Although there are considerable data supporting the role of infections in a pathophysiology of autoimmune diseases, this role has been clearly established in only a few autoimmune diseases.[38] Infectious agents can also cause autoimmune complications by several mechanisms, while the most important mechanisms are molecular mimicry and superantigens.[39] We did not investigate these issues in IgED, and thus can only speculate that the observed frequent infections in our population could trigger autoimmune disorders.[6,7,40]

IgE is a mucosal immunoglobulin, a component of a network of proteins (FcεRI, CD23, and FcεRI binding protein) involved in the signaling response to an allergen/antigen.[41]

Mucosal immunoglobulins (IgA and IgE) can protect the systemic absorption of mucosal antigens, so IgED can hypothetically induce overcoming of self-tolerance mechanisms and development of autoimmunization.[6,17,36] Moreover, it is possible that IgED predisposes to autoimmunity by adversely affecting mast cell survival.[6,42,43]

In the study, we also found that the overall risk of malignancies was significantly higher in subjects with IgED. This association was observed both for epithelial cancers and for hematologic malignancies. Epidemiological studies have suggested inverse associations between allergic diseases and malignancies.[44] IgE directs potent effector cells into tumor tissues with proven tumoricidic activity.[45] Thus, it can be hypothesized that IgE antibodies might physiologically survey malignant cells. The higher rates of malignancies in our patients with IgED might reflect dysregulated antitumor immunity in this population.

Some limitations of the study need to be addressed. First, the prevalence of some diseases may be underestimated in our study because only those having allergy-related symptoms and/or those requesting antiallergy medications were checked for serum total IgE levels. This potential selection bias can impact the results of the study. Second, as a retrospective study, it may suffer from information bias, because of possible inaccurate clinical records, loss to follow-up, and missing data. Regrettably, we have no bacteriological or any other laboratory evidence that chronic rhinosinusitis and otitis media were not bacterial and secondary to the lack of protective IgE antibodies at the external immune compartment.

The measurement of total serum IgE level is a low-cost test, but current guidelines do not endorse its use in clinical practice,[46,47] mostly because most IgED patients are asymptomatic and are identified by finding a laboratory abnormality, without any apparent associated clinical disease. Nevertheless, we suppose that both children and adult patients with chronic rhinosinusitis, recurrent otitis media, and autoimmune diseases should be screened to exclude IgED. In these symptomatic patients undetectable serum total IgE may serve as a marker of immune dysregulation and autoimmunity.

REFERENCES

1. Ishizaka K, and Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. J Immunol 99:1187–1198, 1967.
2. Frazer JK, and Capra JD. Immunoglobulin: Structure and function. In Fundamental Immunology, 4th ed. Paul WE (Ed). Philadelphia, PA: Lippincott-Raven Publishers, 37–74, 1999.
3. Sutton BJ, and Gould HJ. The human IgE network. Nature 366:421–428, 1993.
4. Peat JK, Toelle BG, Dermand J, et al. Serum IgE levels, atopy, and asthma in young adults: Results from a longitudinal cohort study. Allergy 51:804–810, 1996.

5. Pate MB, Smith JK, Chi DS, and Krishnaswamy G. Regulation and dysregulation of immunoglobulin E: A molecular and clinical perspective. Clin Mol Allergy 8:3, 2010.
6. Smith JK, and Krishnaswamy G. Selective IgE deficiency. Available online at www.uptodate.com/contents/selective-ige-deficiency; accessed September 25, 2012.
7. Smith JK, Krishnaswamy GH, Dykes R, et al. Clinical manifestations of IgE hypogammaglobulinemia. Ann Allergy Asthma Immunol 78:313–318, 1997.
8. Schoettler JJ, Schleissner LA, and Heiner DC. Familial IgE deficiency associated with sinopulmonary disease. Chest 96:516–521, 1989.
9. Polmar SH, Waldmann TA, Balestra ST, et al. Immunoglobulin E in immunologic deficiency diseases. I. Relation of IgE and IgA to respiratory tract disease in isolated IgE deficiency, IgA deficiency, and ataxia telangiectasia. J Clin Invest 51:326–330, 1972.
10. Levin TA, Ownby DR, Smith PH, et al. Relationship between extremely low total serum IgE levels and rhinosinusitis. Ann Allergy Asthma Immunol 97:650–652, 2006.
11. Kang HS, Blink SE, Chin RK, et al. Lymphotoxin is required for maintaining physiological levels of serum IgE that minimizes Th1-mediated airway inflammation. J Exp Med 198:1643–1652, 2003.
12. Kawakami T, and Kitaura J. Mast cell survival and activation by IgE in the absence of antigen: A consideration of the biologic mechanisms and relevance. J Immunol 175:4167–4173, 2005.
13. Levy DA, and Chen J. Healthy IgE-deficient person. N Engl J Med 283:541–542, 1970.
14. Ammann AJ, Hong R, and Good RA. Healthy IgE-deficient person. N Engl J Med 283:542, 1970.
15. Waldmann TA, Polmar SH, Balestra ST, et al. Immunoglobulin E in immunologic deficiency diseases. II. Serum IgE concentration of patients with acquired hypogammaglobulinemia, thymoma and hypogammaglobulinemia, myotonic dystrophy, intestinal lymphangiectasia and Wiskott-Aldrich syndrome. J Immunol 109:304–310, 1972.
16. Polmar SH, Waldmann TA, Balestra ST, et al. Immunoglobulin E in immunologic deficiency diseases. I. Relation of IgE and IgA to respiratory tract disease in isolated IgE deficiency, IgA deficiency, and ataxia telangiectasia. J Clin Investig 51:326–330, 1972.
17. Levy Y, Nakum A, Segal N, et al. The association of selective IgA deficiency and IgE hypogammaglobulinemia. Allergy 60: 836–838, 2005.
18. Roa S, Isidoro-Garcia M, Davila I, et al R. Molecular analysis of activation-induced cytidine deaminase gene in immunoglobulin-E deficient patients. Clin Dev Immunol 2008:146715, 2008.
19. Famuyiwa F, and Rubinstein I. Chronic sinopulmonary inflammatory diseases in adults with undetectable serum IgE in inner-city Chicago: A preliminary observation. Lung. 190:291–294, 2012.
20. Cain WA, Ammann AJ, Hong R, et al. IgE deficiency associated with chronic sinopulmonary infection. J Clin Invest 48:12a, 1969 (Abs).
21. Brandtzaeg P, Karlsson G, Hansson G, et al. The clinical condition of IgA-deficient patients is related to the proportion of IgD- and IgM-producing cells in their nasal mucosa. Clin Exp Immunol 67:626–636, 1987.
22. Ostergaard PA. IgA levels, bacterial carrier rate, and the development of bronchial asthma in children. Acta Pathol Microbiol Scand C 85:187–195, 1977.
23. Ishizaka K, Ishizaka T, and Tada T. Immunoglobulin E in the monkey. J Immunol 103:445–453, 1969.
24. Eckl-Dorna J, Pree I, Reisinger J, et al. The majority of allergen-specific IgE in the blood of allergic patients does not originate from blood-derived B cells or plasma cells. Clin Exp Allergy 42:1347–1355, 2012.
25. Tada T, and Ishizaka K. Distribution of gamma E-forming cells in lymphoid tissues of the human and monkey. J Immunol 104:377–387, 1970.
26. Oettgen HC, Martin TR, Wynshaw-Boris A, et al. Active anaphylaxis in IgE-deficient mice. Nature 370:367–370, 1994.
27. Heyman B. IgE-mediated enhancement of antibody responses: The beneficial function of IgE? Allergy 57:577–585, 2002.
28. Krohn IK, Lund G, Frandsen PM, et al. Mast cell FcεRI density and function dissociate from dependence on soluble IgE concentration at very low and very high IgE concentrations. J Asthma 50:117–121, 2013.
29. Koketsu R, Yamaguchi M, Suzukawa M, et al. Pretreatment with low levels of FcεRI-crosslinking stimulation enhances basophil mediator release. Int Arch Allergy Immunol 161(suppl 2):23–31, 2013.
30. Zhang N, Holtappels G, Gevaert P, et al. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. Allergy 66:141–148, 2011.
31. Turner H, and Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature 402(suppl):B24–B30, 1999.
32. Urb M, and Sheppard DC. The role of mast cells in the defence against pathogens. PLoS Pathog 8:e1002619, 2012.
33. Tokura Y, Sugita K, Kabashima K, Ito T, Yagi H. Alopecia universalis associated with impaired interleukin-4 production and low serum IgE level. J Am Acad Dermatol 57(suppl):S22–S25, 2007.
34. Minuk GY, Boyd ND, Matheson DS, et al. Serum immunoglobulin E levels in patients with primary biliary cirrhosis. J Allergy Clin Immunol 83:462–466, 1989.
35. Wang N, Shen N, Vyse TJ, et al. Selective IgA deficiency in autoimmune diseases. Mol Med 17:1383–1396, 2011.
36. Liblau RS, and Bach JF. Selective IgA deficiency and autoimmunity. Int Arch Allergy Immunol 99:16–27, 1992.
37. Cunningham-Rundles C. Autoimmune manifestations in common variable immunodeficiency. J Clin Immunol 28(suppl 1): S42–S45, 2008.
38. Ercolini AM, and Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol 155:1–15, 2009.
39. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest 108:1097–1104, 2001.
40. Sfriso P, Ghirardello A, Botsios C, et al. Infections and autoimmunity: The multifaceted relationship. J Leukoc Biol 87:385–395, 2010.
41. Davies JM, and O'Hehir RE. Immunogenetic characteristics of immunoglobulin E in allergic disease. Clin Exp Allergy 38:566–578, 2008.
42. Kitaura J, Song J, Tsai M, et al. Evidence that IgE molecules mediate a spectrum of effects on mast cell survival and activation via aggregation of the FcepsilonRI. Proc Natl Acad Sci U S A 100:12911–12916, 2003.
43. Lu LF, Lind EF, Gondek DC, et al. Mast cells are essential intermediaries in regulatory T-cell tolerance. Nature 442:997–1002, 2006.
44. Wang H, and Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 60: 1098–1111, 2005.
45. Fu SL, Pierre J, Smith-Norowitz TA, et al. Immunoglobulin E antibodies from pancreatic cancer patients mediate antibody-dependent cell-mediated cytotoxicity against pancreatic cancer cells. Clin Exp Immunol 153:401–409, 2008.
46. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 122(suppl):S1–S84, 2008.
47. Kerkhof M, Dubois AE, Postma DS, et al. Role and interpretation of total serum IgE measurements in the diagnosis of allergic airway disease in adults. Allergy 58:905–911, 2003. □